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ANIMAL-MODEL STUDIES OF RADIATION-INDUCED EMESIS AND ITS CONTRO--ETC(U)
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Robert E. Cordts, Major, USAF, BSC

August 1982

Interim Report for Period January 1974 - January 1981

USAF SCHOOL OF AEROSPACE MEDICINE
Aerospace Medical Division (AFSC)
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NOTICES

This interim report was submitted by personnel of the Dynamic Effects Branch, Radiation Sciences Division, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas, under job order 7757-05-38.

When Government drawings, specifications, or other data are used for any purpose other than a definitely Government-related procurement, the United States Government incurs no responsibility or any obligation whatsoever. The fact that the Government may have formulated or in any way supplied the said drawings, specifications, or other data, is not to be regarded by implication, or otherwise in any manner construed, as licensing the holder, or any other person or corporation; or as conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)* This paper reviews all work conducted by or for personnel of the Radiation Sciences Division, USAF School of Aerospace Medicine, on the subject of radiation-induced emesis. Emesis is considered primarily as a facet of the prodromal syndrome which indicates that a person may have received sufficient radiation to provoke performance decrement of some degree. The subjects were adult male dogs. Four radiation sources were used, and doses ranged between 140 and 800 rad. An orderly progression of work led to the identification of three drugs		

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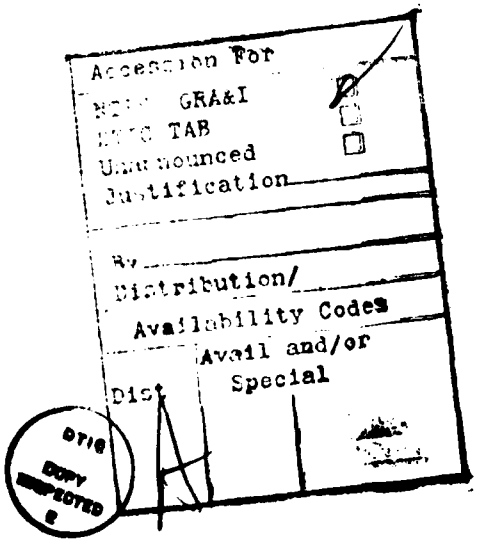
20. ABSTRACT(continued)

that, given together 30 minutes prior to cobalt-60 irradiation, raised the emetic threshold about 90%. One experiment, however, suggested that these same drugs may have little benefit when neutron irradiation is used.



ANIMAL MODEL STUDIES OF RADIATION-INDUCED EMESIS AND ITS CONTROL

BACKGROUND

In the early 1970s, Strategic Air Command specifically requested development of medication, a pill, to counter acute radiation effects that affect performance. In response to that request, personnel of the Radiation Sciences Division, U.S. Air Force School of Aerospace Medicine (USAFSAM), reinitiated select investigations of biomedical effects of radiation. Where previous studies had pursued negating lethal effects of radiation, the new work aimed at understanding radiation-induced performance decrements. With that knowledge investigators hoped to develop medications to extend a person's ability to perform work adequately. In the first investigation in this line, radiation effects on the cardiovascular system were studied (1). That was our first attempt to understand radiation-induced hypotension which is one element of the prodromal syndrome.

Other elements of the syndrome include anorexia, nausea, vomiting, diarrhea, malaise, and fatigue (2). Due to variability among individuals, most elements of the syndrome are unpredictable in their occurrence or degree of effect. Vomiting, however, is representative of the syndrome and is quantitative. Under certain conditions of flight-related work, vomiting is itself a critical performance problem and may even be life threatening. Most of our work in acute effects of radiation, however, has evolved to studying emesis as an indicator of having received sufficient radiation to lead to performance problems.

The investigator must carefully consider the best species to use to answer the question under study. Although many types of good performance data are available from radiated monkeys, the question in this series of studies deals with identifying the quantity of radiation leading to the prodromal syndrome and how to combat the resultant effects. Dogs rather than monkeys have been used as our primary test subjects for these emesis studies for the following reasons (see Table 1): 1) The dog's LD_{50} is closer to the estimate of man's LD_{50} than is the monkey's (3,5,6). 2) The dog's ED_{50} compares more closely to man's than does the monkey's (4,5,7). 3) The time to onset is more similar between dog and man than monkey and man (4,5,7). 4) Monkeys can have retching without emission of vomitus; it is extremely difficult to know if this is unproductive retching or is vomiting in which material may have been contained in the cheek pouches and then swallowed.

TABLE 1. MONKEY-MAN-DOG COMPARISONS

	LD_{50} (rad)	ED_{50} (rad)	Onset (min)	Ref.
Monkey:	530			3
		446	41	4
Man:	245-286	183-214	144	5
	250	181		6
Dog:	230			5
		170	112	7

TWO STUDIES OF EMESIS FROM CANINE PARTIAL-BODY EXPOSURE TO X-RAYS

In the first emesis study, conducted in 1976, the effectiveness of various pharmacologically active drugs was tested against abdominal radiation in dogs (8). The commercially available drugs listed in Table 2 were selected for known antiemetic activity or as blockers of CNS mechanisms possibly involved in radioemesis. Drugs were given no more than 75 minutes before exposure, based on their biologic half-life. The drug dosage levels, subject sample sizes, and significant results of a positive nature are given in Table 2. The tranquilizer and antihistamines were effective in several quantitative areas.

TABLE 2. ANTIEMETIC TESTING OF COMMERCIALLY AVAILABLE DRUGS

Compound & Dose	Function (Subjects)	Significant Results	Drug	Control
Dimenhydrinate 50 mg	Antihistamine Anticholinergic (12)	Fewer episodes	3.1 ± 1.8	6.6 ± 2.6
		Longer time to onset (min)	90 ± 22	46 ± 23
Diphenhydramine 25 mg ÷2[a]	Antihistamine Anticholinergic (13)	Fewer episodes	3.8 ± 1.7	6.6 ± 2.6
		Longer time to onset and shorter duration (min)	92 ± 33	46 ± 23
			61 ± 28	118 ± 50
Chlorpromazine 50 mg ÷2	Tranquilizer (13)	Fewer episodes	2.8 ± 1.9	6.6 ± 2.6
		Longer time to onset and shorter duration (min)	112 ± 38	46 ± 23
			56 ± 38	118 ± 50
Phenytoin 60 mg ÷2	Anticonvulsant (12)			
Perphenazine 4 mg	Antipsychotic (12)			
Amphetamine 10 mg plus scopolamine 0.6 mg	Sympathomimetic competitive of acetylcholine (13)			
Acetyl salicylic acid 2 g ÷2	Antiprostiglandin Analgesic Antiinflammatory (12)			
WR 2721 75 mg/kg ÷2	Radioprotective (7)			

[a] ÷2 indicates that this total drug quantity was given in two doses during preexposure time frame.

This study and the next utilized a Picker Model 736 X-ray source. Its settings were 200 kVp and 25 mA. With a 0.25-mm copper filter and inherent filtration, the radiation had a half-value thickness of 1.1-mm copper. Dogs were lightly anesthetized with methoxyflurane and restrained in a body cast for the exposures. Bilateral exposure through 10- x 10-cm portals in the body cast provided a total of 800 rad at the midline at the rate of 50 rad per minute.

Since catecholamine receptor neurons had been strongly indicated as being involved in radiation-induced emesis, the second study (9) was designed again using dogs as subjects. Injected chemicals were intended 1) to reduce synthesis of catecholamines (alpha-methyl-paratyrosine, or α-MPT) or 2) to effect a chemical sympathectomy (6-hydroxydopamine, or 6-OHDA) that would interrupt the catecholamine-mediated pathway of induction of vomiting.

Table 3 shows the drugs, number of subjects, dosage schedule, and results of this study. The result of 6-OHDA was similar to that of haloperidol, one action of which is catecholamine receptor neuron blocking. The fact that 6-OHDA works strictly at these catecholamine neurons provides further evidence that catecholaminergic neurons are involved in radiation emesis.

TABLE 3. ANTIEMETIC TESTING OF EXPERIMENTAL COMPOUNDS

Compound & Dose	Function & Subjects	Significant Effect
Alpha-methyl-paratyrosine (α-MPT) 114 mg/kg i.v. 60 minutes preexposure	Reduces synthesis of catecholamines n = 13	None
6 hydroxydopamine (6-OHDA) 2 mg/kg i.v. 30 minutes preexposure	Chemical sympathectomy n = 12	Reduced number of emetic episodes Delayed onset times
Haloperidol 0.25 mg/kg i.m. 45 minutes preexposure	Catecholamine blocker n = 13	Reduced number of emetic episodes Delayed onset times

TWO STUDIES TO DETERMINE DRUG CONTROL OF COBALT GAMMA-INDUCED EMESIS

The next question we attempted to answer was how effective are specific approved drugs in reducing radioemesis (7). Attention to the side effects of drugs under consideration was a primary factor in developing the protocol. A drug capable of reducing radiation-induced decrement, but which itself caused incapacitation, would be of no benefit. Because of its strong tranquilizing action, chlorpromazine was eliminated from further testing.

After a careful search, thiethylperazine was selected as a proven antiemetic that seemed to have most tranquilizing properties removed. Similarly, promethazine was selected to represent anticholinergic and, more importantly, antihistamine groups. Specifically, promethazine is an antihistamine of the H_1-type, and cimetidine represents the H_2-type antihistamines. Naloxone was selected for its function as a narcotic antagonist previously shown to inhibit the emetic action of apomorphine on the chemoreceptor trigger zone (10).

The dosages (see Fig. 1) were established as high or higher than approved for human use for any therapeutic reason so that the testing would be biased toward succeeding. The dogs were injected and observed for motor deficits or coordination problems before radiation exposure.

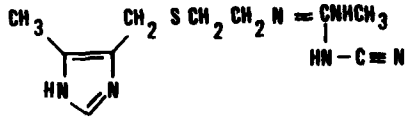
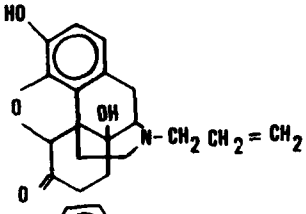
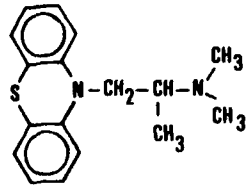
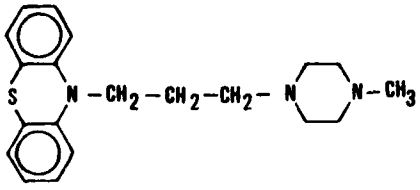
COMPOUND & DOSAGE	STRUCTURE	FUNCTION
CIMETIDINE 4 mg/kg		COMPETITIVE ANTAGONIST OF ACTIONS OF HISTAMINE AT H_2 RECEPTORS
NALOXONE 0.08 mg/kg		ANTAGONIST OF MORPHINE-LIKE OPIOIDS
PROMETHAZINE 2 mg/kg		ANTICHOLINERGIC AND H_1 HISTAMINE ANTAGONIST
THIETHYLPERAZINE 0.86 mg/kg		ANTIEMETIC EFFECTIVE AGAINST A WIDE RANGE OF EMETIC STIMULI

Figure 1. Drugs tested for effectiveness in reducing radioemesis in dogs (Cooper-Mattsson study). Promethazine and thiethylperazine are both phenothiazine derivatives, so their structures are similar.

Our radiation source for these studies was the AECL Eldorado 78 cobalt-60 unit at Brooks Air Force Base. In 1978, the source was reloaded to 9500 Ci. All exposures were unilateral (to the left side) to unanesthetized, male, random-source dogs at the rate of approximately 65 rad per minute. Doses were all measured at the midline.

The up-down technique (11) was used for emesis-threshold testing. In this technique, sampling intervals (step sizes) are estimated to be one standard deviation. A sample must be completed during testing because the result is used to establish the testing level for the next subject. Figure 2 graphically illustrates results in the control group in this experiment. The dog tested at 500 rad vomited during the 10-hour observation period; therefore, the next dog to be exposed in this group received 450 rad. That dog also vomited; the following dog therefore received one step less radiation.

This process continued until, at 200 rad, a dog failed to vomit; then the radiation level was raised one step for the next dog. In this manner once the mean is reached, testing will fluctuate around the mean. The up-down technique is excellent for determining 50% effect and does so with fewer samples than does probit sampling, but does not yield as good estimates of ED_{10} or ED_{90}.

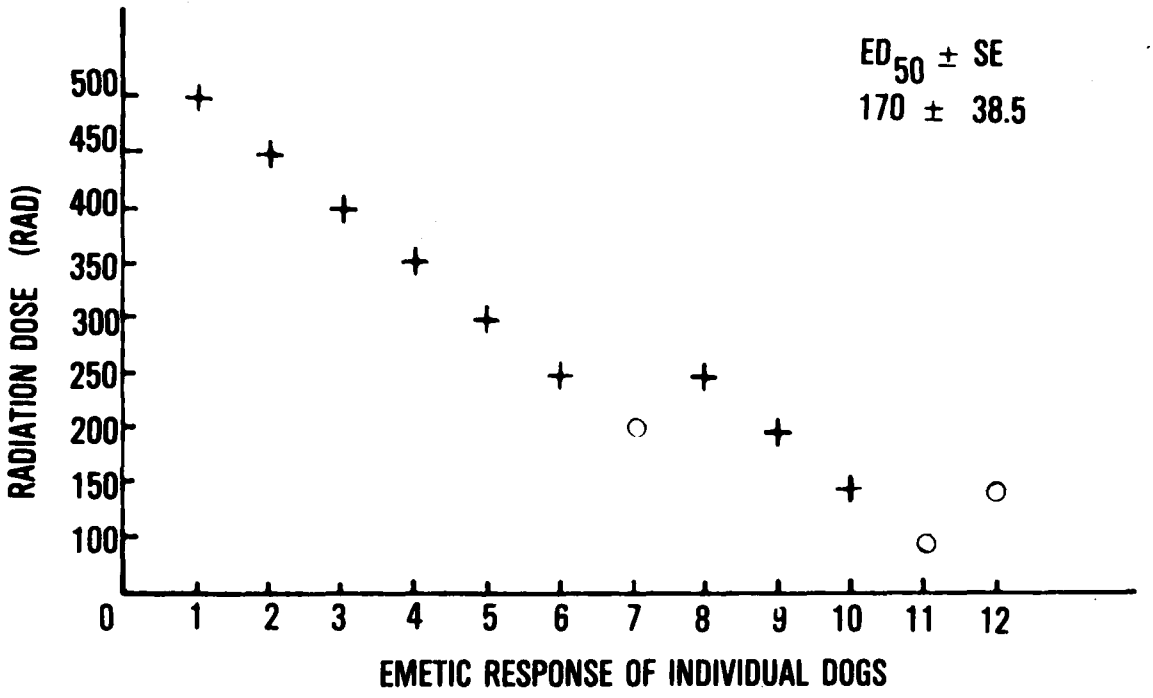


Figure 2. Results of emesis-threshold testing in 12-dog control group (Cooper-Mattson study, up-down testing technique). Each point represents one dog: + indicates that the dog vomited during the observation period; o, that he did not. Statistical computations were based on 7 samples (dogs).

Based on the small-sample technique (11), to develop the statistics associated with this test, the experimenter used only one sample unit before the reversal plus all following samples. Figure 2 shows that the first unit prior to reversal is the first dog at 250 rad. Thus the dogs included in statistical computations total seven samples. Statistics were computed to show the 50% effectiveness point, or ED_{50}, and the standard error (SE). For the control group (with which we were working), that was 170 $\pm$ 38.5 rad.

The drugs were tested in a similar manner. Each drug was tested in a group of dogs and the statistics were computed after that testing. The ED_{50}

and SE results for each group of dogs are graphed in Figure 3. Cimetidine, promethazine, and thiethylperazine were statistically significant in raising the quantity of radiation required to produce vomiting. Naloxone was not and therefore was removed from further testing programs. This work demonstrated the value of drugs in raising the threshold of radiation-induced emesis and provided a good basis on which to build follow-on experiments.

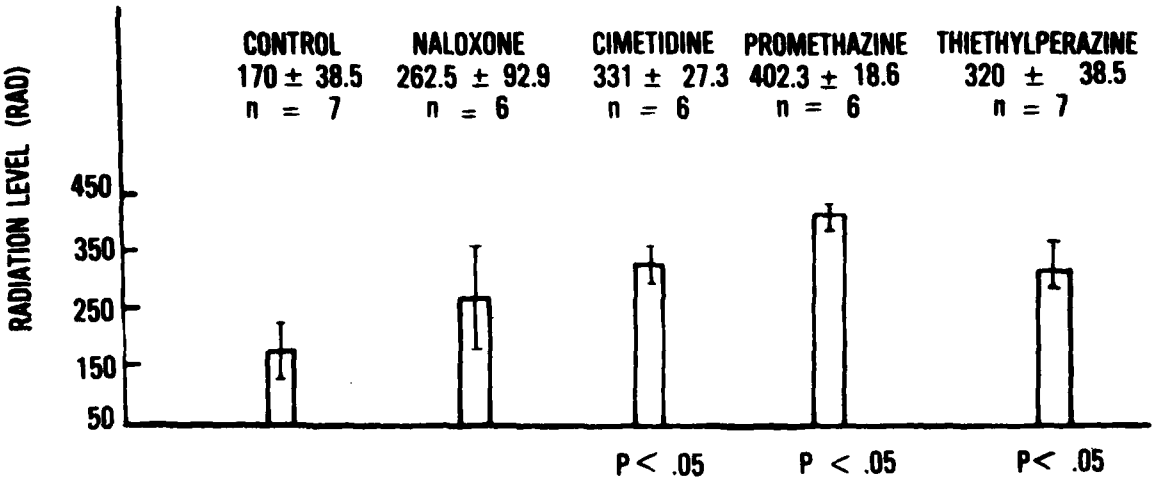


Figure 3. Radiation required to produce vomiting in drug-treated and control groups of dogs (Cooper-Mattson study, ED_{50} ± standard error). Three of the drug-treated groups were significantly different when compared to the control (untreated) group. (N = number of dogs in statistical computations.)

The second study was conducted to determine the value of the three effective drugs at more reasonable doses and see if combining the drugs would be beneficial (12). These drugs are all available for oral administration, an added benefit. The dosage was changed and was calculated on a milligram per square meter (mg/m^2) basis (see Table 4). Cimetidine was increased since the FDA-approved dose had been increased during the ensuing year and that drug is not considered to be centrally active. The quantity was too great for intramuscular injection, so cimetidine was given intravenously (as in the first study). With combined drugs, the same amount of each drug was administered as indicated for the single doses.

The first study was used as a pilot; as a result, the radiation intervals for the second study were established on a logarithmic basis: the closer to zero rad, the smaller the steps. This makes testing more sensitive at the lower doses and prevents using many animals to look for reversals at higher doses. Since no emetic activity occurred after 8 hours in the first study, the observation period for this study was set at 8 hours.

TABLE 4. DRUG DOSAGES FOR ANTIEMETIC STUDY

Treatment	Dosage	Subjects	Remarks
Control	------	31	
Cimetidine (Cim)	167 mg/m^2 i.v.	25	Approx 60% increase in dose over first study
Promethazine (Pro)	13.92 mg/m^2 i.m.	25	Dosage 25% of first study
Thiethylperazine (Thi)	5.57 mg/m^2 i.m.	25	Dosage 25% of first study
Cim + Pro	As above	25	
Cim + Thi	As above	25	
Pro + Thi	As above	25	
Cim + Pro + Thi	As above	25	

Results are depicted in Figure 4. When irradiated controls were c ed to drug-plus-irradiation groups, four statistically significant groups determined by Tukey's simultaneous test procedures. With this experime. ne ED_{50} of the dog drew closer to its LD_{50} (just as primate ED_{50} and LD_{50} are

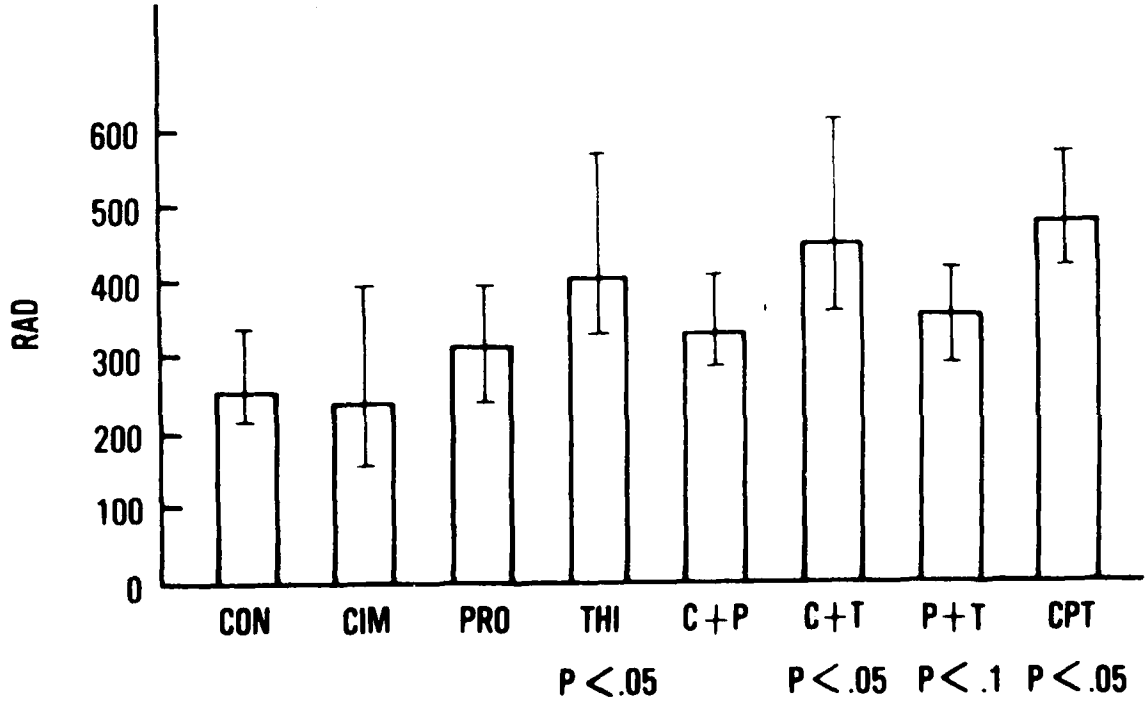


Figure 4. Comparison of control (irradiated) group with groups receiving antiemetic drugs (alone and combined) plus irradiation (Mattsson-Cordts study, ED_{50} and 95% confidence intervals based on up-down testing).

quite close). Cimetidine was not significantly beneficial at 167 mg/m^2 and surprisingly had a much wider variability--represented by the 95% C.I.--than seen in the previous study. The variability for the other drugs given singly was also greater. However, the variability of any two drugs combined was less than either of the drugs used alone. And the variability of the cimetidine-promethazine-thiethylperazine combination was quite tight, much better than the cimetidine-thiethylperazine combination and slightly less than either of the other two-drug combinations. The random chance of all of this happening is very low (about 0.7%).

Data recorded during observations included emesis onset time, number of retches per episode, and number of episodes. Conclusion of the last episode represents the offset time; thus, we can obtain duration.

Several different manipulations of the data follow, each demonstrating an important feature. As seen in Figure 4, the ED_{50} and 95% confidence interval were established for each group. Next we added only emetic responders from each group together to obtain a ninth group. In these we compared dependent responses by correlation coefficients. As itemized in Table 5, at the 0.05 level negative correlation was significant between onset times and number of episodes as well as between onset times and duration of vomiting; positive correlation was significant between number of episodes and duration time.

TABLE 5. CORRELATIONS OF EMESIS DATA FROM RESPONDERS ONLY

		Drug-treated Groups							
Group	Cont	Cim	Pro	Thi	C+P	C+T	P+T	CPT	All
Radiation range (rad)	206-446	170-368	250-446	303-545	250-446	303-545	303-446	368-658	170-658
Responders	12	14	11	12	12	12	12	13	98
Correlations									
Episodes to onset times	-.39	-.48	-.44	-.76*	-.50	-.70*	-.48	-.66*	-.46*
Episodes to duration	.39	.83*	.38	.84*	.83*	.93*	.60*	.76*	.58*
Onset time to duration	-.32	-.64*	-.38	-.78*	-.53	-.56	-.59*	-.88*	-.46*

*Significant at $\alpha = .05$ (two tailed)

TABLE SUMMARY

Significant Correlations	Groups Significant	Groups Compared
Early onset times are associated with more episodes.	4	9
More episodes imply longer duration times.	7	9
Later onset times occurred with shorter durations.	5	9

The pattern of increasing episodes as radiation increased, of numbers of episodes in treated and untreated dogs, and of duration compared in treated and untreated dogs are all important observations. Based on these data, the correlations noted, and the fact that most dogs were treated with a statistically significant antiemetic, a strong statement can be made: "In dogs, the severity of radiation sickness is not dramatically affected by treatment once a subject becomes a responder." This agrees with, and tends to explain, results of blind clinical trials of antiemetics and placebos in radiation therapy patients.

THREE STUDIES COMPARING NEUTRON- TO GAMMA-INDUCED EMESIS

Using neutrons, we tried to duplicate the work of the cobalt studies. Our studies compared reactor-source gamma (n:γ ratio of 1:14) to neutrons (n:γ ratio of 8.5:1) in causing emesis in dogs (13). In this work, accomplished at the Armed Forces Radiobiology Research Institute (AFRRI), we did a small study in 1979 and a larger one, including testing of the combination of three drugs, in 1980.

Testing followed the up-down technique and was intended to repeat, as closely as possible, the procedure used in the cobalt studies. Subjects were awake, male, random-source dogs. For the studies at AFRRI, their TRIGA reactor was used. Exposures were bilateral and doses received were measured at the midline. For the primarily gamma exposures, the beam was moderated through 12 inches of water; exposures were made at 70 rad per minute. For the primarily neutron exposures, the beam traversed a 6-inch-thick wall of lead; exposures were made at 120 rad per minute.

Figure 5 represents the results of these two studies. The results of both the gamma and neutron exposures show a considerable difference between years, as well as much more variability than from the cobalt studies. In addition to the wide disparity of results between 1979 and 1980, the animals treated with our three-drug combination and exposed to neutrons yielded very frustrating results. Apparently the drugs had no benefit after the dogs were exposed to neutron irradiation: the treated and control ED_{50}s are very similar at about 380 rad. Also, a great variability was seen within the treated group; this was not anticipated from our cobalt exposures.

A short study was conducted using the GODIVA reactor at White Sands Missile Range, New Mexico (14). Fifty-five male random-source dogs were irradiated--five groups of 11 each, selected in a random manner. These conscious dogs were exposed unilaterally. (A control group of 10 dogs received no irradiation.) Each group was given a different level of pulsed irradiation between 220 and 728 rad. The low dose was expected to produce little or no emesis in dogs, but the 728-rad dose was considered very likely to produce emesis in most. The remaining doses were chosen as dividing the difference on a logarithmic basis. Filtration was not attempted; the neutron:gamma ratio was about 9:1, and the pulse required 50 µsec.

This analysis procedure, the probit technique, lends itself to a more definite estimate of ED_{10} and ED_{90} levels of effect. Emesis results are seen in Table 6. In this series of exposures, the ED_{50} was 318 rad and the ED_{10} and ED_{90} were 67 and 570 rad respectively. However, approximately 40% of the animals were subjected to movement due to gusting winds during observation.

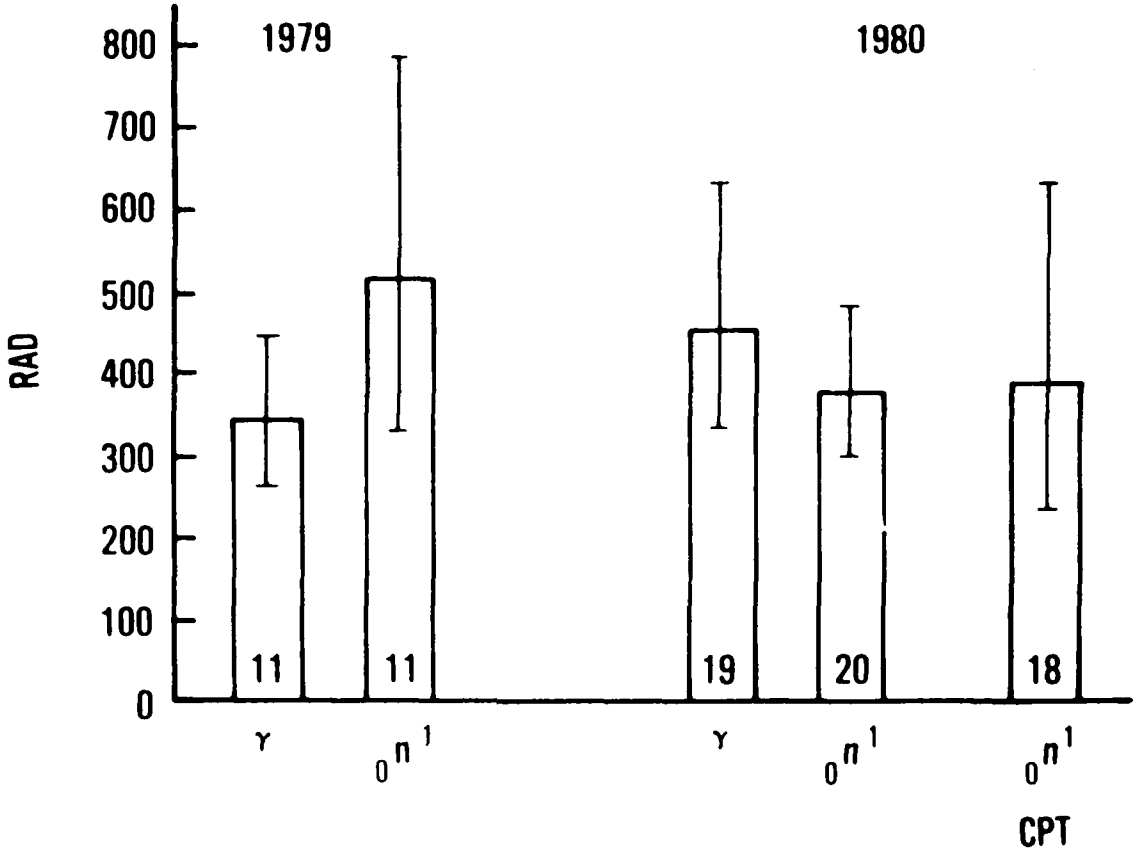


Figure 5. Comparison of gamma- and neutron-induced emesis in untreated and drug-treated dogs (ED_{50} and 95% confidence interval based on up-down testing). The 1979 study was to compare responses to reactor-source gamma and neutron irradiation; the 1980 study tested also the effectiveness of drugs to raise the neutron emetic threshold.

TABLE 6. EMESIS IN DOGS EXPOSED TO PULSED NEUTRONS

Radiation (rad)	Subjects	No. vomiting
0	10	0
220	11	4
296	11	4
400	11	8
540	11	9
728	11	11

ED_{10} = 67 rad; ED_{50} = 318 rad; ED_{90} = 570 rad

Motion may be an important aspect of radiation-induced emesis, depending on conditions and timing. An unrelated study (4) had been designed to determine the ED_{50} of cobalt-60-induced vomiting in rhesus monkeys; the ED_{50} was 446 rad. Six other monkeys were tested with radiation and motion together; that ED_{50} was 258 rad. These monkeys were placed in a chair that oscillated forward and backward 5^{o} to 15^{o} in a random fashion at a maximum rate of 0.3 Hz. The motion-plus-radiation ED_{50} is a significant reduction ($p \leq 0.01$) from that of radiation alone and occurred in a species that is rarely affected by motion alone.

CONCLUSIONS

Four radiation sources have been used in these studies conducted under the supervision and/or effort of USAFSAM Radiation Sciences Division personnel. Table 7 annotates the similarities and differences between the sources and procedures in irradiation of dogs.

TABLE 7. VARIOUS EXPOSURE CONDITIONS USED WITH DOGS

Location	Mason Research Worchester, MA	Brooks AFB San Antonio, TX	AFRRI Bethesda, MD	White Sands Missile Range, NM
Type	Picker Model 736 X-ray	AECL Eldorado 78, cobalt-60	TRIGA MARK F Reactor	GODIVA Reactor
Characteristics	200 kVp 25 mA .25-mm Cu filter 1.1-mm Cu half-value layer 50 rad/min	9500 Ci in 1978 65 rad/min	n:γ 1:14 thru 12" H_2O 70 rad/min n:γ 8.5:1 thru 6" Pb 120 rad/min	n:γ 8.9:1 50-μsec pulse
Exposure conditions	Restraint by methoxyflurane anesthesia Bilateral to 10- X 10-cm portal mid abdomen	Restraint in Plexiglas box Unilateral to left side whole body (except head usually)	Restraint in Plexiglas box Bilateral to whole body	Restraint in aluminum mesh box Unilateral to left side whole body
Fed	60 min post irradiation	60 min pre irradiation	100 min pre irradiation	60 min pre irradiation
Antiemetic drugs	30-75 min pre irrad	30 min pre irrad	45 min pre irrad	None
Dose at midline	800 rad	Varied, 140-658 rad	Varied, 220-836 rad	Varied, 220-728 rad

The studies have demonstrated that in dogs exposed to gamma radiation, the radioemetic threshold can be raised by drugs; also, a combination of proper drugs is more effective in raising the threshold than are the same drugs when given singly.

Better characterization of radiation-induced emesis in animals is another benefit from this work. The dog appears to be a very good model of human radioemesis. In the irradiation range of 200-800 rad, more severe exposure leads to more severe prodromal effects. Specifically, as radiation dose increases, onset time decreases and number of episodes and duration of vomiting increase.

Another factor of note is that rather severe motion reduced, almost by half, the amount of radiation required to cause emesis in rhesus monkeys, in spite of the fact that the species is not a good model of motion sickness. The human, on the other hand, certainly is susceptible to the malady.

Nuclear weapons radiation, even without compounding elements, would be expected to cause emesis at quite low doses in some humans. Drugs have been shown to increase the emetic threshold in dogs; however, when emesis does occur in the treated dog, it is about as severe as it would have been had the animal not been treated. These investigations were made with careful consideration that side effects of the drugs, considered alone, be as small as possible. Effects of these drugs on performance by the unirradiated human have yet to be determined. Until proper testing makes drugs available to counter radiation effects, performance of many Air Force jobs will become more difficult if people are exposed to radiation.

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